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Minimally Invasive Surgical Device for Precise Application of Bioadhesives to Prevent iPPROM

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Keywords
iPPROM · Minimally invasive therapy · Fetoscopy · Fetal endoscopy · Bioadhesives · Application · Umbrella

Abstract
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Introduction

With advances in fetal diagnosis and therapies, in specialized centers fetoscopy has become a real therapeutic option to treat potentially life-threatening diseases during pregnancy. However, this invasive intervention into the amniotic cavity is associated with a significant risk of preterm rupture of membranes leading to preterm birth resulting in fetal morbidity and mortality [1]. Preterm birth is mainly due to the injury of the fetal membranes, which do not to heal spontaneously after surgical injury [2–5]. The risk of an iatro-

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genic preterm prelabor rupture of fetal membranes (iPPROM), which happens in up to 30% of all fetoscopies [1], affects a significant number of pregnant women worldwide. Therefore, it is generally accepted that preventive sealing and stabilization of fetal membranes could significantly extend pregnancy and thus drastically improve fetal health and survival.

In contrast to reports indicating potential fetal membrane healing signals in vitro [6–8], ex vivo and in vivo investigations showed a very limited success towards membrane healing and did not show any evidence of decreasing the risks of membrane rupture [9–17]. Platelet concentrate, in combination with cryoprecipitate or industrially available fibrin glue, was reported to be a potential effective amniotic membrane sealant [18–21]. However, positive performance of platelet injection was accompanied with extensive platelet production and provoked fetal death in some reported cases [22].

More recently, the development of mussel-inspired adhesives working in wet environments brought new hopes for the efficient closure of the fetal membrane [23–25]. Indeed, this glue showed good sealing potential in vitro [24, 26], ex vivo [25], and in rabbit models in vivo [23].

Despite a multitude of candidate glues for membrane sealing, there is an obvious lack in a reliable method to deposit these liquid sealing materials on the inside of the amniotic cavity at the exact site of membrane defect. This study aims to establish a method to seal fetal membrane defects by accessing the wound through the port used during fetoscopy. To achieve this aim, the focus was set on developing a minimally invasive device able to deliver a gluing material in a very controlled and localized manner at the site of fetal membrane puncture.

Materials and Methods

Our approach to prevent iPPROM relied on the combination of 3 elements: (a) an umbrella for the collection of adhesive materials, (b) an applicator to introduce the umbrella, and (c) an injection system to deliver adhesive materials inside the cavity of the umbrella. All these elements were assembled in one single device enabling to carry out the sealing procedure in 5 short steps. The idea was to insert the umbrella through the fetoscopy port, deploy it inside the amniotic cavity, bring it back to the uterine wall and glue the umbrella onto the fetal membrane. The port will be removed after applying the glue while the glued umbrella stays in place until delivery of the placenta. This method enables the sealing of the defect without further detachment of the fetal membrane from the decidua and avoids the need of an additional hole for the application of the adhesive.

Device Components for the Preventive Sealing of Fetal Membranes

Umbrella for the Collection of Sealing Materials

The polyester fabric-coated mesh was designed in an umbrella shape and is responsible for collecting the gluing materials at the site of puncture in a shielded environment. It is composed of 2 elements: a nitinol backbone and a membrane covering that backbone in order to keep the adhesives in place and prevent the glue from flowing into the amniotic fluid. Nitinol is a very elastic FDA-approved metallic alloy that possesses unique shape memory properties enabling spontaneous unfolding of the umbrella into its original shape upon exit of the catheter [27]. The nitinol stripe thickness was set at 200 μm, and the umbrella-shaped height at 3 mm. Those characteristics gave a mechanical resistance to the umbrella to enable the surgeon to feel a resistance before its flattening or even everting when pulled against the fetal membrane. The umbrella backbone was composed of 8 identical oval ribs, each connected to the neighboring one, forming a circular shape. This circular design directed the tight folding of the umbrella into a shape smaller than the 10-Fr port (Fig. 1a, b). They were produced by laser cutting followed by temperature-based shape setting.

To cover the nitinol backbone, Degrapol®, a polyester urethane polymer fabric, was used given its high stretchability and elasticity [28]. Besides its ideal mechanical characteristics, it has previously shown good biocompatibility and capacity to integrate into rabbit fetal membranes and promote reepithelialization [9]. To make those fabrics, we first produced 150-μm-thick Degrapol® sheets. To do so, 600 mg of lyophilized Degrapol® was dissolved in 3.52 g of chloroform and 0.88 g of hexafluoroisopropanol to make 5 g of 12% Degrapol® mix. The solution was left at room temperature overnight, and 2 mL of this solution was electro-spun at a rate of 1 mL per hour on 12 glass slides rotating on the collector. The distance between the syringe needle and the collector was 10 cm. The resulting Degrapol® sheets were removed from the glass slides by immersing in 30% ethanol. The nitinol mesh was sintered between 2 Degrapol® sheets to get a stable composite.

Applicator and Injector

A stainless-steel tube with an outer diameter of 2.9 mm and inner diameter of 2.7 mm was designed and manufactured (Fig. 1c, applicator). This tube slides freely in the 10-Fr catheter and is tight enough to push the umbrella (Fig. 1c, umbrella) through the port. A double-chamber tube connected to its glue injector (Duplocath 180; Baxter AG, Volketswil, Switzerland) from the Tisseel® glue pack was inserted into the hollow tube from the proximal to the distal end to ensure that the 2 glue substrates only merge at the distal end of the tube into the umbrella. The proximal end (Fig. 1c, glue injector) permitted the separate injection of the 2 glue precursors.

The umbrella must remain attached to the applicator in order to prevent it from getting lost in the amniotic cavity upon deployment and to allow the pulling against the fetal membrane defect. To do so, we attached a thread to the center of the umbrella and connected it to a locking system at the distal part of the applicator. Upon unlocking this system by the user, the thread is set free, and the umbrella detached from the applicator.

Bioadhesives

To test the fetal membrane sealing procedure, Histoacryl® (B. Braun Surgical AG, Melsungen, Switzerland), fibrin glue (Tis-

seel®; Baxter AG, Volketswil, Switzerland), and mussel glue [29–33] were employed. Histoacryl® is a cyanoacrylate-based, Federal Drug Administration (FDA)-approved, one component glue that polymerizes upon contact with hydroxyl ions present in wet environments. Histoacryl® was directly transferred from its ampoule to a syringe tube before application. Fibrin and mussel glue are sealants that readily polymerize upon mixing of the 2 polymer precursors. Mussel glue was previously shown to have very good properties for the sealing fetal membranes under wet conditions [25, 26]. As previously described, the polymer substrate is dissolved in 2× PBS and mixed in a 1:1 volume ratio to 12 mg/mL sodium periodate for a final mussel glue concentration of 150 mg/mL.

Human Fetal Membranes

Human fetal membranes were collected from patients with written consent following the decision from the Ethical Committee of the District of Zürich (study Stv22/2006). Fetal membranes were harvested after caesarian section at term (between 37 and 39 weeks) and frozen at –80 °C until use. All of them were negative for HIV, hepatitis B, diabetes mellitus, chlamydia, and group B streptococci.

Mechanical Testing

Mechanical Stability of the Umbrella

The mechanical stability of the umbrella (Fig. 1a) was assessed by measuring the force needed to completely flatten the umbrella. A thread was attached to the stock of the umbrella at the concave side. The thread was then pulled until the umbrella was flattened and the force needed to do so was measured with a dynamometer (Pesola AG, Schindellegi, Switzerland, Ref. DO29/FH27). Umbrellas with and without Degrapol® fabric were pulled on solid (Petri dish) and soft surfaces (1.5-cm-thick bovine muscle) (n = 5).

Adhesion Strength Provided by Bioadhesives to Glue the Umbrella to Intact Fetal Membranes

Intact, dry fetal membranes were flattened on a Petri dish with the amnion facing up. The umbrellas were placed on top of the fetal membrane followed by the injection of 500 µl of adhesives inside the umbrellas through a syringe and allowed to polymerize for 5 min. The adhesion strength between fetal membrane and umbrellas provided by the glues was measured with a dynamometer by pulling the umbrellas perpendicularly to the membrane surface (n = 5 for each adhesive).

Application and Gluing of Umbrella on Punctured Fetal Membranes

Dry Experimental Conditions

A fetal membrane was mounted onto an empty plastic cup with the amnion facing downward to the interior of the cup. A very high bonding elastomeric membrane (3M AG, Rüschlikon, Switzerland) was punched with a 6-mm diameter biopsy punch and deposited onto the fetal membrane on the plastic cup model. To quantify the mechanical stability, we measured the force needed to pull up the center of the mounted fetal membrane by 1.5 cm with a dynamometer.

Complete ex vivo Fetal Membrane Defect Model

To simulate the intervention, we created a physiologically relevant ex vivo model. Porcine skin containing a small muscle layer with a total thickness of 0.5 cm was chosen to mimic the upper abdominal wall. A bovine muscle of 1 cm thickness and a human fetal membrane were added under the "abdominal wall" to mimic the uterus layer. Those 2 layers, together with the human fetal membranes, were put together, stretched, placed onto an 8-cm diameter aluminum cylinder and tightly clamped in a watertight manner by screwing a ring on top (Fig. 2). Saline solution was added inside the cylinder to mimic amniotic fluid and the leftover air was removed by side ports of the aluminum cylinder. A 5-mm cut was made with a scalpel on the skin mimic to facilitate the access to underlying tissues. To quantify the mechanical stability, we measured the force needed to pull up the center of the model by 1.5 cm with a dynamometer. Two inlets in the cylinder enabled the cylinder to be filled with solutions reproducing the amniotic fluid. Another inlet permitted the insertion of a video-intubation system (Acutronice Medical Systems AG, Switzerland) to enable visual control over the placement of the umbrella. The time needed for each step of the procedure was measured.

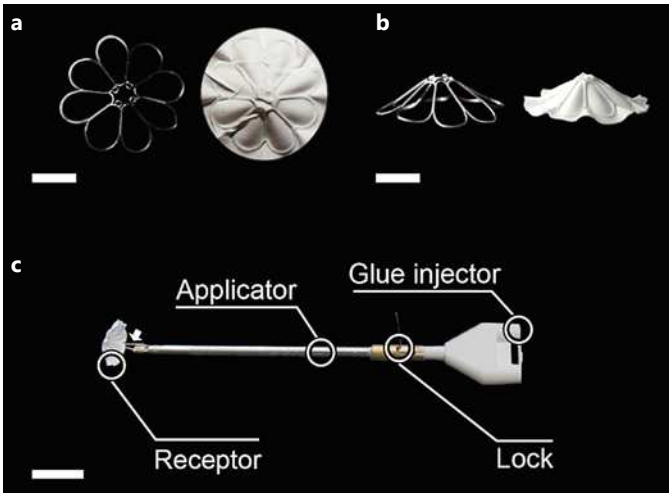

Fig. 1. Photographs of the device's components. Top view (**a**) and side view (**b**) of the umbrella-shaped receptor without (left) and with (right) Degrapol® membrane coverage. Scale bars, 5 mm. **c** Applicator device prototype in its open conformation. The applicator is responsible for pushing the umbrella inside the 10-Fr introducer (not shown). The glue injector is the entry site for the glue, which is delivered to the umbrella with the assistance of a double-chambered tube placed inside the applicator. Scale bar, 15 mm. The release mechanism of the umbrella is controlled by one small metallic wire going through the applicator (lock). When in the locked position, the wire traps the suture wire connected to the umbrella. When in the unlocked position, the suture wire is no longer trapped and the umbrella can be disconnected from the applicator.

Defect Sealing

A 10-Fr port (Check-Flo Performer® Introducer; Cook Medical, Bloomington, IN, USA) was mounted on the obturator (Anklin AG, Switzerland) and inserted through the tissue mimic in a

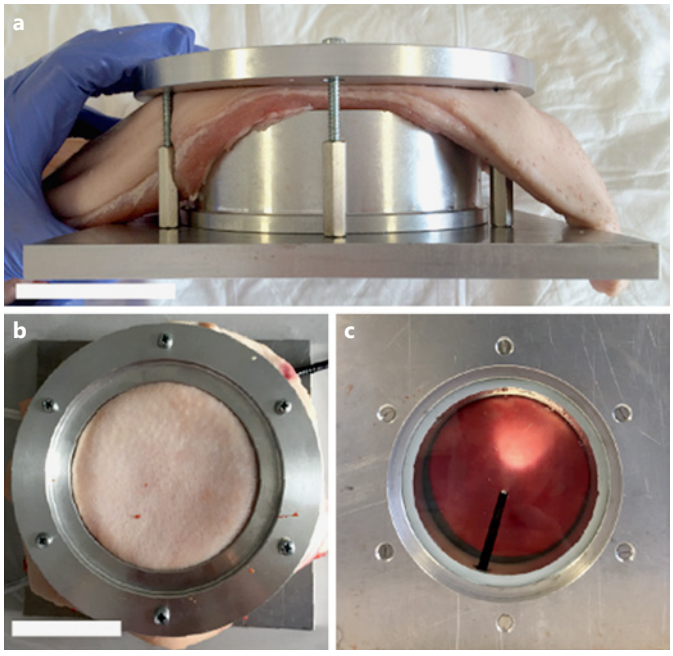

Fig. 2. Ex vivo fetal membrane model. Side view (**a**), top view (**b**), and bottom view (**c**) of the tissue clamped in the aluminum cylinder. Scale bars, 5 cm.

45° angle. The obturator was removed and the port left in the defect. The umbrella was tightly folded and inserted in the port before pushing it into the cavity filled with saline solution. The umbrella was pulled against the membrane, and 500 µL of mussel glue, fibrin glue or Histoacryl® (100 µL corresponding to the dead volume of the double-chamber injection channel plus 400 µL adhesive) was perfused through the injector into the umbrella using syringes connected to the injection inlets. Polymerization was allowed for 1 min while the umbrella was held against the fetal membrane in its umbrella-shaped conformation. After the intervention, membranes were unmounted from the aluminum cylinder and turned upside down. The umbrella was pulled perpendicularly to the membrane surface and the force needed to remove the umbrella from the membrane was measured with a dynamometer.

Results

Umbrella for Adhesive Collection

The evaluate the umbrella's shape stability we compared the force resistance of its nitinol backbone with the complete umbrella consisting of the nitinol backbone and the covering membrane. In addition, we performed this assay on a plastic Petri dish or on a 1.5-cm-thick muscle layer, which aims to determine the impact of the support on which the umbrella is measured. While the backbone on the stiff and the soft surface deformed at almost identical forces of 0.21 ± 0.02 N and 0.2 ± 0.02 N, respectively, the resistance to deformation of the full umbrella was significantly increased on both soft and stiff substrates (Fig. 3). The force for flattening was significantly higher on the solid substrate (0.33 ± 0.02 N) as compared to the soft substrate (0.25 ± 0.02 N). This indicates that the umbrella needs to be tested with the membrane on a soft tissue to ensure the relevance of the assay for its in vivo application. Finally, the applicator was shown to slide through the 10-Fr catheter with minimal force (0.2 ± 0.02 N) and access the inside of the amniotic cavity.

Adhesion Strength of the Umbrella to Intact Fetal Membranes

In the first step, we evaluated the potential of 3 adhesive candidates to glue the Degrapol®-coated umbrellas to dry, intact fetal membranes to select the best-matching adhesive for further testing. The measured adhesion forces of the umbrellas to the fetal membranes showed that mussel glue reached similar gluing properties as Histoacryl® (0.83 ± 0.2 N and 1.1 ± 0.17 N, respectively, $n = 5$), while fibrin with 0.2 ± 0.14 N ($n = 5$) exhibited very weak binding (Fig. 4a, dark grey bars). As a drawback, Histoacryl® had the effect of drying out both the fetal and Degrapol® fabrics, discarding it as candidate for the next experiment.

Application and Gluing of the Receptor on Fetal Membrane Defects under Dry Experimental Conditions

Next, we assessed the reliability of our method in dry experimental conditions in the plastic cup model. We used our device to insert the umbrella and deliver the adhesives to glue the receptor on the fetal membrane defect. In all the assays, the receptors adhered to the fetal membrane following adhesion and release. However, all the glues showed different strengths of adhesion. Histoacryl® resisted up to 0.96 ± 0.38 N ($n = 3$) of pulling force until detachment, compared to 0.35 ± 0.12 N ($n = 5$) and 0.17 ± 0.18 N ($n = 5$) for mussel glue and fibrin, respectively (Fig. 4a, light grey bars). In all the cases ($n = 13$), the umbrellas deployed to their initial shape, were placed tightly on the fetal membrane and no leakage of the glue was observed upon injection. In addition, the measure of mechanical stability of the model showed a force of 0.1 N for a displacement of 1.5 cm.

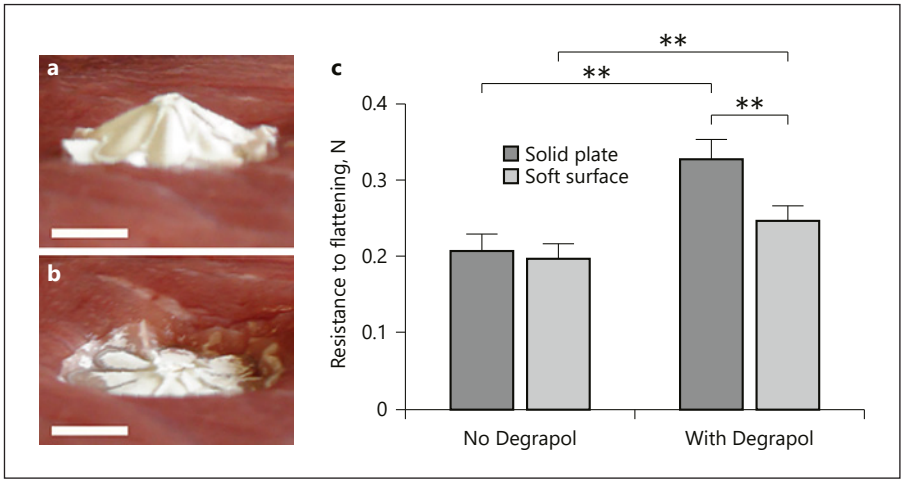

Fig. 3. Shape stability of the receptor. Umbrella-shaped receptor with Degrapol® membrane on bovine muscle (soft surface) before pulling test (**a**) and during pulling test (**b**). Scale bars, 5 mm. **c** Force needed to flatten the receptor ($n = 5$; ** $p < 0.02$).

Fetal Membrane Defect Sealing Procedure on Complete ex vivo Model

Defect Sealing ex vivo

To conclude the proof of feasibility of the approach, we simulated the defect sealing on a more clinically relevant model and observed the procedure from the inside of the cavity with an endoscopic camera (Fig. 5). While the addition of saline solution simulated the amniotic fluid, the multiple layers improved anatomical resemblance and improved mechanical stability. Indeed, the displacement test assessing the mechanical stability showed a force of 1 N required for the displacement of 1.5 cm. Mussel glue was chosen due to its suited applicability in wet environments and its non-cytotoxicity. In all trials ($n = 5$), the umbrella opened into its original shape and was properly placed onto the defect. The glue was well confined in all the umbrellas despite some observations of minimal leakage. These were mainly due to the slight permeability of the Degrapol® and to the excessive volume of adhesive injected. However, this never impaired the adhesion of the umbrella to the fetal membranes. Indeed, all the umbrellas held onto the fetal membranes upon release and removal of the applicator. The adhesion strength gluing the umbrella to the fetal membrane was on average 0.13 ± 0.04 N.

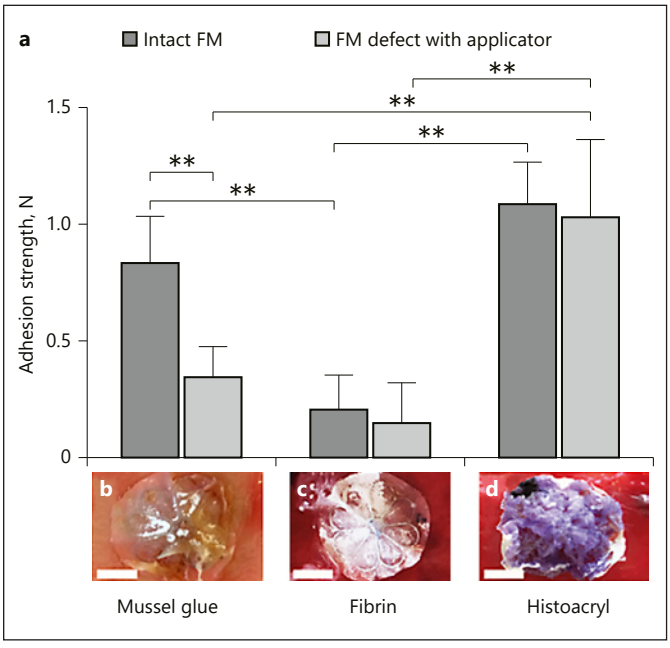

Fig. 4. Gluing of umbrellas to fetal membranes. The histogram (**a**) shows adhesion strengths of umbrellas glued to fetal membranes with mussel glue (**b**; dark grey $n = 5$; light grey $n = 5$), fibrin glue (**c**; dark grey $n = 5$; light grey $n = 5$) or Histoacryl® (**d**; dark grey $n = 5$: light grey $n = 3$). Dark grey bars represent the cases where the receptors were directly glued on intact fetal membranes. The photos show representative images of umbrellas when glued onto intact fetal membranes. Scale bars, 5 mm.

Time of Procedure

Time intervals needed for each part of the intervention are summarized in Table 1. Device application, which included tightly folding the umbrella and placing it onto the fetal membrane, was the longest step of the procedure with an average of 1 min and 28 ± 43 s. Glue injection time had a constant 1 min polymerization period in all the tests, to which 27 ± 7 s was needed to place the syringes on the glue injection inlets and apply the glue. Finally, 13 ± 9 s were added to activate the locking system and release the umbrella. In summary, the total

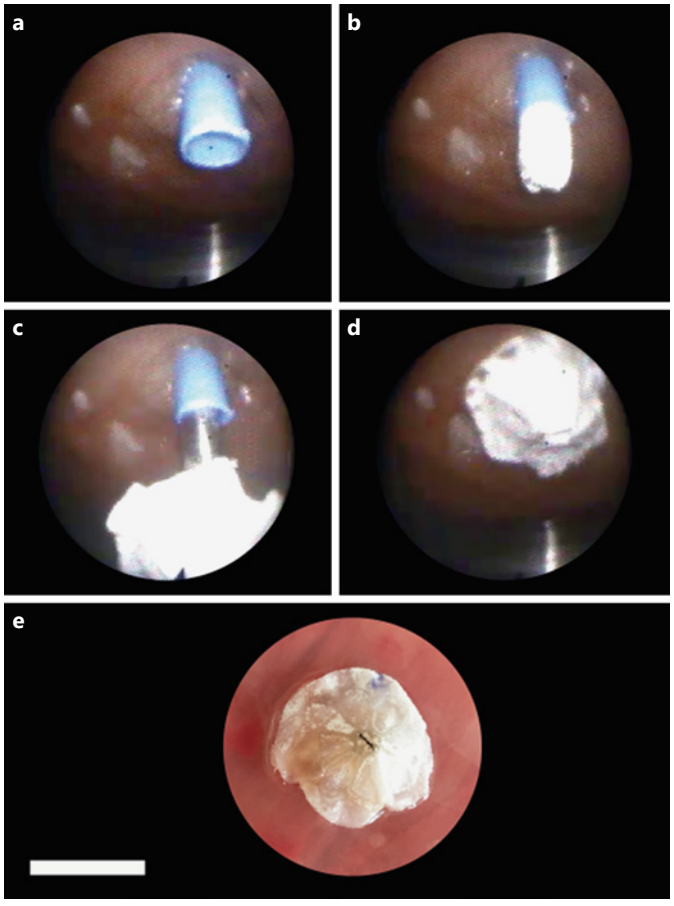

Fig. 5. Ex vivo fetal membrane defect sealing procedure. **a–e** The procedure from the inside of the cylinder, reproducing the view from the amniotic cavity. **a** Accession of the catheter (blue tube) right after punching through the construct to create the defect. The white element shows the umbrella in its tightly folded conformation being introduced (**b**), deployed (**c**), and pulled against the amnion (**d**). **e** Mussel glue was absorbed by the Degrapol®, changing its color to red. The figure shows the umbrella glued onto the fetal membrane after dismantling. Scale bar, 5 mm.

average time for the whole procedure was 3 min and 8 s, which represents an insignificant increase in time for fetoscopy.

Discussion

In this study, we developed a novel method to preventively seal fetal membrane defects by a minimal invasive procedure and succeeded in proving its feasibility. We demonstrated it by developing a model reproducing close to real anatomic conditions and by delivering gluing materials at the site of membrane puncture in a controlled manner, which is believed to be the key for efficient membrane sealing. Indeed, previous studies showing the deposition of hydrogel materials or blood coagulation-derived materials lacked a controlled method specifically designed for this matter [9, 12, 15–17, 20, 34]. The deliberate choice of diverse sealing materials – 2-component glues like fibrin or the promising mussel glue [23–26] and Histoacryl® – was done to demonstrate the compatibility of our device with materials of different natures and to highlight the relevance of our method for the testing of those injectable candidates. As follows, we discuss more in detail the elements that make the device presented here a serious option to be considered for the application of sealing or even healing agents at the site of fetal membrane puncture.

Table 1. Statistics of the fetal membrane sealing procedure

	Time, min:s	Success rate
Device application	1:28±0:43	5/5 (100%)
Glue injection	1:27±0:07	5/5 (100%)
Umbrella release	0:13±0:09	5/5 (100%)

Umbrella

The umbrella was easily folded into the port, slid freely through the port and always deployed automatically into the defined shape. The mechanical stability assessed by the pulling test against a hard or a soft surface indicated that the nitinol backbone stability needs to be measured with the fabric covering the metallic structure and on a soft surface in order to have relevant data translatable to the in vivo situation. In addition, the relatively low resistance force (0.25 N) suggests that structural changes might be needed to increase this value up to a palpable resistance (0.5–1 N) but without impairing the folding capability of the umbrella. The reason for that would be to enable the surgeons to feel the moment when applying the umbrella onto the fetal membrane. This can be done by increasing the nitinol thickness and varying the number of struts.

As for the fabric covering the nitinol backbone, Degrapol® met the expectations for glue collecting, but its use for further investigations is limited to non-cyanoacrylate glues. The use of an alternative solution to cover the nitinol backbone could potentially tackle this burden. For example, with expanded polytetrafluoroethylene (ePTFE), an FDA-approved polymer used for example in her-

nia repair [35], fabrics with important elastic and nonpermeable properties could be generated, corresponding to the functional requirements of our application. This polymer can also be electrospun and is already used to cover nitinol stents in some applications [36]. The clinical use of ePTFE has also been done in combination with Histoacryl® sealant for ePTFE graft fortification [37], which speaks in favor of combining those materials in future investigations. In addition, Histoacryl® and other cyanoacrylate-based glues are routinely used in vivo for eyelid skin grafts without complications [38]. Similar to ePTFE, silicone can provide equal mechanical properties. Its use in combination with nitinol for thoracoamniotic or vesicoamniotic shunts makes it a good candidate for our application [39]. However, further investigation is required to determine the best adhesive candidates to combine with silicone.

Umbrella Adhesion to Fetal Membranes

We first aimed to assess the inherent ability of different glues to bind the umbrellas to fetal membranes, which is the sine qua non for their successful use to prevent iPPROM. The glues used in this study showed different characteristics. Fibrin was not efficient in any test and barely any adhesive force was measurable. Mussel glue and Histoacryl® showed a very good performance when glued on intact fetal membrane, which confirms the potential of those glues to be used as sealants on fetal membranes. Similarly to previous studies [26], Histoacryl® presented the strongest bonding efficiency throughout the study, but the binding strength correlated with dissolution of Degrapol®, encouraging once again its replacement with a more compatible material like silicone or ePTFE.

Procedure Simulation on an ex vivo Model

Finally, we chose the adhesive that was previously shown to have a significant potential to work in wet environment and did not have a destructive effect on Degrapol®. We increased the complexity of the assays by recreating the wet environment of the amniotic cavity inside the cylinder and recapitulated the abdominal and uterine wall with ex vivo tissues. This was necessary to increase by 10-fold the mechanical support provided by the whole tissue mimic compared to the elastomeric model (1 vs. 0.1 N), which granted the model an increased physiological relevance.

All the umbrellas were well positioned and collected glue successfully. The measure of the strength of attachment showed relatively low adhesion force of mussel glue (0.13 ± 0.04 N) but all stayed tight to the fetal membranes after umbrella release. However, the data showing the adhesion strength of mussel glue on intact membranes in dry conditions indicate that mussel glue has the potential to confer strong adhesion. Different improvements might influence the adhesive strength. For example, a mixer could be added at the distal part of the applicator to pool the glue substrates better together. Alternatively, the optimization of the volume and/or viscosity of the adhesive could significantly help increase adhesion strength by improving fluid dynamics at the amnion and umbrella surfaces.

As a next step, the feasibility of the method and the right use of materials will need to be tested on in vivo models. This is necessary to assess (a) the applicability of the umbrella in real conditions and (b) the behavior of the implant in real conditions in a longer time span. Additionally, such experiments will indicate if after delivery the umbrella remains attached to the uterine wall and needs to be removed by curettage.

Time of Procedure

Furthermore, the whole procedure took approximately 3 min, which is a determinant factor when adding up a step in the surgical procedure. This time span can be further decreased with training, experience and by starting the procedure with the umbrella already tightly folded inside the tube, making the time factor a negligible element for the adoption of the method.

Conclusion

We fruitfully designed and produced a functioning device facilitating the controlled deposition of bioadhesives for prophylactic sealing of fetal membrane defect after fetoscopic interventions. Our data indicate that the application method can reliably be used to precisely inject gluing materials and seal the punctured amnion from the inside of the cavity. This study also highlighted the need of an alternative material for the umbrella fabric and for stronger adhesives. We believe that those elements can be improved in a further step with alternative materials already existing in the industry. Regardless of the adhesives used, the results proved the feasibility of our method to successfully place an umbrella that collects bioadhesives for the closure of fetal membrane defects while respecting the geometrical requirements imposed by fetoscopic intervention instruments. We are thus convinced that this method has a future in the prevention of iPPROM and opens a new horizon in prenatal treatment.

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Disclosure Statement

There are no conflicts of interest.

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